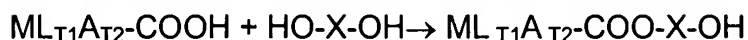


AMENDMENTS TO THE CLAIMS:

Please amend Claims 1 – 38 as follows:

1. (Currently Amended) A process for the ~~manufacturing~~ manufacture of NO-donating compounds comprising;~~step-4~~ (1),



(I)

(II)

using an acidic or dehydrating agent and a first solvent, optionally followed by purification using extraction or ~~crystallisation~~ crystallization, and



(II)

(III)

using a second solvent, a base and optionally a catalyst, followed by purification using extraction and ~~crystallisation~~ crystallization, and

~~step-3~~ (3),



(III)

(IV)

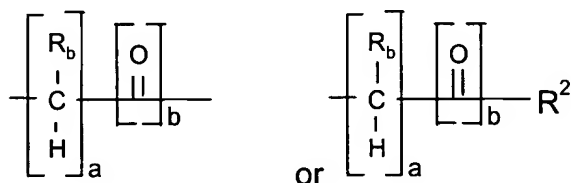
using a third solvent and optionally a catalyst,

optionally followed by a ~~crystallisation~~ crystallization process for obtaining the compound of formula IV in a substantially crystalline form, and

wherein:

M is a radical of a physiologically active compound;

L is O, S, (CO)O, (CO)NH, (CO)NR¹, NH, NR¹, wherein R¹ is a linear or branched alkyl group, or



wherein R_b is H, C₁₋₁₂alkyl or C₂₋₁₂alkenyl;

R² is (CO)NH, (CO)NR¹, (CO)O, or CR¹ and a and b are independently 0 or 1;

A is a substituted or unsubstituted straight or branched alkyl chain;

X is a carbon linker;

R is selected from the group consisting of C₁-C₈ alkyl, phenyl, phenylmethyl, C₁-C₄ alkylphenyl, halophenyl, nitrophenyl, acetaminophenyl, halogen, CF₃ and *n*-C₄F₉;

Y-NO₃ is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zinc nitrate ~~or~~ and tetraalkylammonium nitrate, ~~[[()]]wherein alkyl is a~~
straight or branched C₁-C₁₈-alkyl, ~~which may be straight or branched~~;

m is 1 or 2; and

T₁ and T₂ are each independently 0, 1, 2 or 3;

with the proviso that

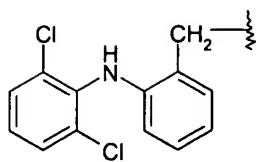
when ML_{T₁}A_{T₂}-COOH is naproxen, then X is not (CH₂)₄.

2. (Currently Amended) The process according to claim 1, wherein group M is part of a molecule of an NSAID, COX 1 or COX 2 inhibitor.

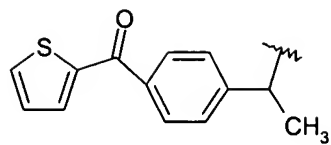
3. (Currently Amended) The process according to claim 1, wherein X is selected from the group consisting of linear -(CH₂)_{w1}, wherein w1 is an integer of from 2 to 6; -(CH₂)₂-O-(CH₂)₂ and -CH₂-C₆H₄-CH₂.

4. (Currently Amended) The process according to claim 1, wherein R is selected from the group consisting of C₁-C₈-alkyl, phenyl, phenylmethyl, C₁-C₄-alkylphenyl, halophenyl, nitrophenyl, acetaminophenyl, and halogen.

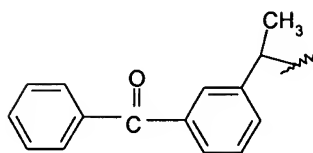
5. (Currently Amended) The process according to claim 1, wherein the group ML_{T₁}A_{T₂} is selected from the group consisting of:



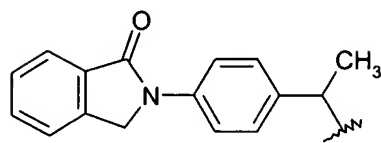
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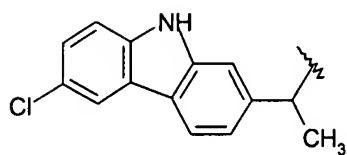
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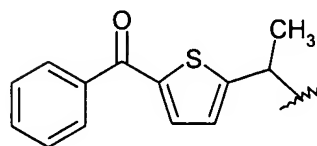
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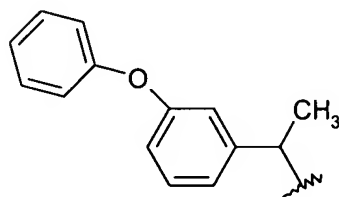
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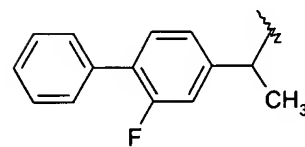
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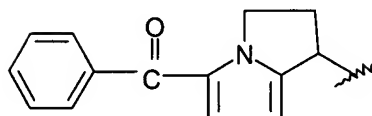
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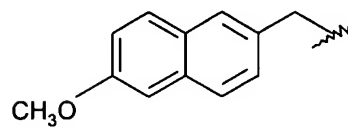
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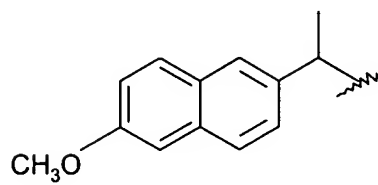
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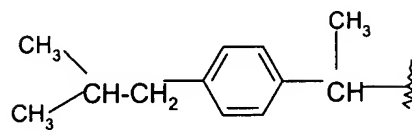
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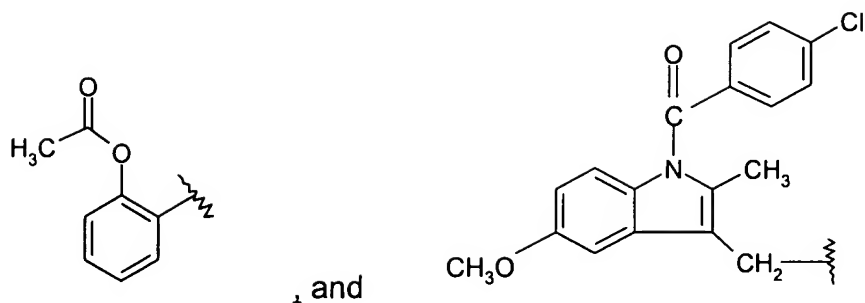
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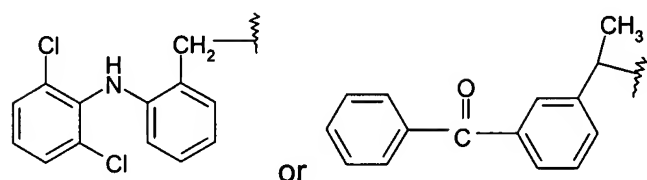
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1



6. (Currently Amended) The process according to claim 5₁ wherein the group ML_{T1}A_{T2} is:



7. (Currently Amended) The process according to ~~any one of claims 4 to 6~~ claim 1, ~~whereby wherein~~ the ~~crystallisation~~ crystallization process for the compound of formula IV comprises ~~the following steps:~~

- a) i) dissolving the compound in a fourth solvent;
- or,
- ii) extracting the compound from the reaction solution into a fourth solvent;
- or,
- iii) starting from the reaction solution comprising said the compound;
- b) ~~vaporating~~ evaporating the fourth solvent;
- c) adding an anti-solvent and/or cooling
- d) isolating the crystals formed, and optionally;
- e) ~~recrystallising~~ recrystallizing the crystals formed ~~in step c); or isolated in step d).~~

8. (Currently Amended) The process according to claim 7, ~~whereby wherein~~ the ~~crystallisation~~ crystallization process for compound 2-[2-(nitrooxy)-ethoxy]ethyl{2-[(2,6-dichlorophenyl)amino]phenyl}acetate (IVa) comprises ~~the following steps:~~

- a) extracting the compound from the reaction solution into a the fourth solvent;

- b) evaporating the fourth solvent;
- c) adding an anti-solvent and/or cooling;
- d) isolating the crystals formed, and optionally;
- e) ~~recrystallising~~ recrystallizing the crystals formed ~~in step c);~~ or isolated in step d).

9. (Currently Amended) The process according to ~~any one of claims 1 to 8~~ claim 1, whereby an wherein the acidic or dehydrating agent ~~in step 1~~ is selected from the group consisting of sulphuric acid or its salts, perchloric acid (e.g. 70%) ~~or other suitable acids such as~~ polystyrene sulphonic acids, zeolites, acidic clays, sand in combination with strong hydrophilic acids, ~~such as perchloric acid or gaseous hydrogen chloride and montmorillonites.~~

10. (Currently Amended) The process according to ~~any one of claims 1 to 8~~ claim 1, whereby wherein the first solvent ~~in step 1~~ is a non-polar and/or non acidic solvent.

11. (Currently Amended) The process according to ~~any one of claims 1 to 10~~ claim 1, whereby wherein the second solvent is ~~solvents in step 2~~ are selected from a group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate, and isopropyl acetate.

12. (Currently Amended) The process according to ~~any one of claims 1 to 10~~ claim 1, whereby wherein the base in step 2 is triethylamine or *N*-methyldimorpholine.

13. (Currently Amended) The process according to ~~any one of claims 1 to 10~~ claim 1, whereby wherein the catalyst in step 2 is 4-(dimethylamino)pyridine.

14. (Currently Amended) The process according to ~~any one of claims 1 to 13~~ claim 1, whereby wherein the compound of formula III in step 2 is ~~crystallised~~ crystallized from an organic solvent.

15. (Currently Amended) The process according to claim 14, ~~whereby~~ wherein an ~~antisolvent~~ anti-solvent is used in the crystallization of compound of formula III in ~~step 2~~.

16. (Currently Amended) The process according to ~~any one of claims 1 to 15~~ claim 1, ~~whereby the nitrate sources~~ wherein Y-NO₃ in ~~step 3~~ is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, and calcium nitrate, ~~or~~ and mixtures thereof.

17. (Currently Amended) The process according to ~~any one of claims 1 to 15~~ claim 1, ~~whereby~~ wherein the third organic solvent in ~~step 3~~ is selected from the group consisting of N-methylpyrrolidinone, sulpholane, tetramethylurea, 1,3-dimethyl-2-imidazolidinone, acetonitrile, methyl isobutylketone, ethyl acetate, butyl acetate, and isopropyl acetate, ~~or~~ and mixtures thereof.

18. (Currently Amended) The process according to ~~any one of claims 1 to 15~~ claim 1, ~~whereby~~ wherein the phase transfer-catalyst in ~~step 3~~ is selected from the group consisting of tetraalkylammonium salt, arylalkylammonium salt, tetraalkylphosphonium salt, arylalkylphosphonium salt, crown ether, pentaethylene glycol, hexaethylene glycol, and polyethylene glycols, ~~or~~ and mixtures thereof.

19. (Currently Amended) The process according to ~~any one of claims 7 or 8~~ claim 7, ~~whereby~~ wherein the fourth solvent in ~~step a)~~ is selected from the group ~~comprising~~ consisting of lower alkyl acetates, lower alkyl alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, heteroaromatic hydrocarbons, dialkyl ketones, dialkyl ethers, nitriles, and water, ~~or~~ and mixtures thereof.

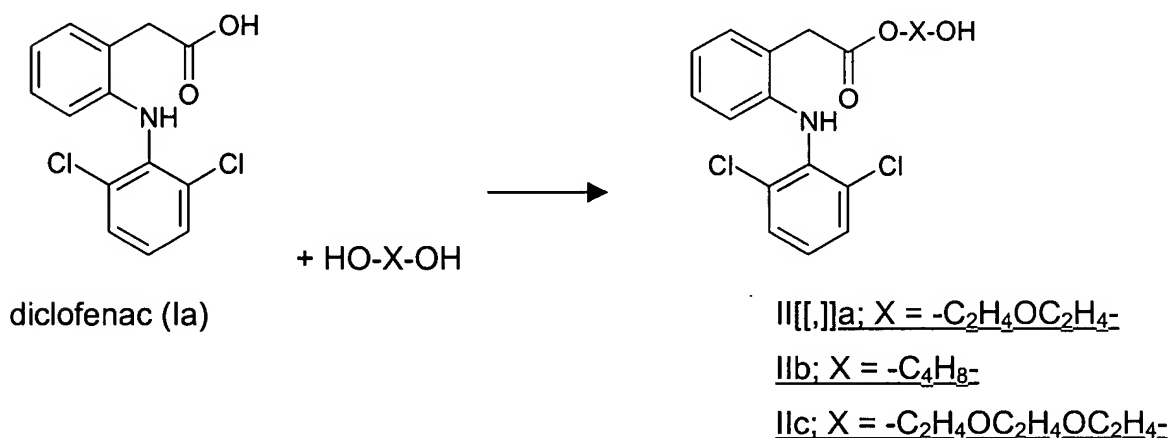
20. (Currently Amended) The process according to ~~any one of claims 7 or 8~~ claim 7, ~~whereby~~ wherein the anti-solvent ~~the antisolvent in step b)~~ of the crystallisation process is selected from the group ~~comprising~~ consisting of ethanol, ~~or~~ 2-propanol,

toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes, and cycloheptanes, or and mixtures thereof.

21. (Currently Amended) The process according to ~~any one of claims 7 or 8~~ claim 7, whereby wherein the solvent in step d) is selected from the group consisting of toluene, cumene, xylenes, methyl *iso*-butyl ketone, di-*n*-butyl ether, *tert*-butyl methyl ether, tetrahydrofuran, acetonitrile, *n*-butyl acetate, and dichloromethane, or and mixtures thereof.

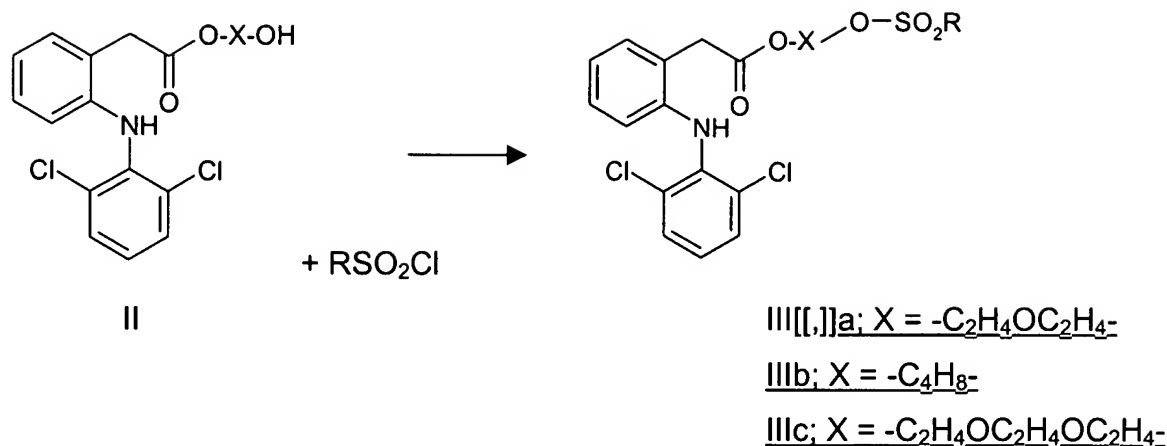
22. (Currently Amended) The process according to ~~any one of claims 1 to 21~~ claim 1, whereby wherein the process is conducted at a temperature is between -40°C and 120°C.

23. (Currently Amended) A process for the ~~manufacturing~~ manufacture of NO donating diclofenac of formula IVa, IVb or IVc, comprising:
~~step 1 (1)~~, reacting a compound of formula Ia with HO-X-OH, wherein X is C₂H₄OC₂H₄, C₄H₈, or C₂H₄OC₂H₄OC₂H₄, to obtain compounds of formula IIa, IIb or IIc,



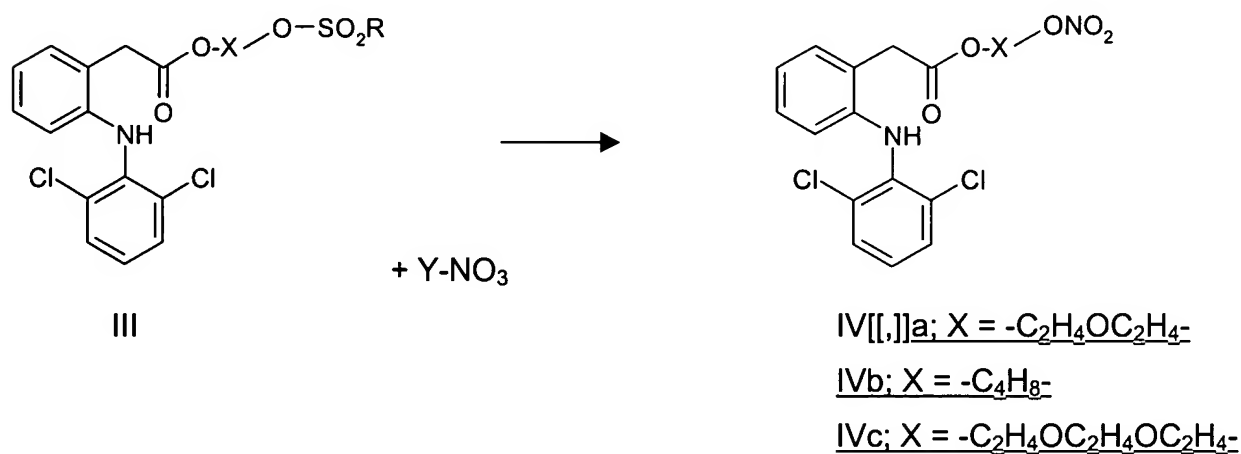
~~followed by,~~

~~step 2 (2)~~, reacting the compounds of formula IIa, IIb or IIc with RSO₂Cl, wherein R is as defined ~~above~~ in claim 1, to obtain compounds of formula IIIa, IIIb or IIIc,



~~followed by,~~

~~step 3~~ (3), reacting the compounds of formula IIIa, IIIb or IIIc with a nitrate source Y-NO₃, wherein Y is as defined ~~above~~ in claim 1, to obtain compounds of formula IVa, IVb or IVc,



~~followed by,~~

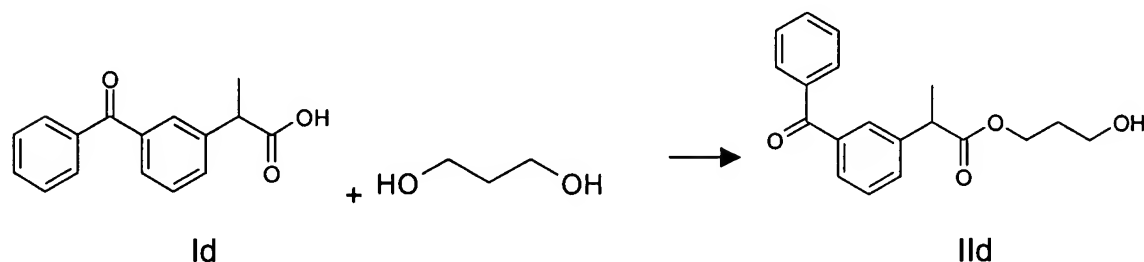
~~crystallising~~ crystallizing the compounds of formula IVa, IVb or IVc using ~~the following~~ steps by:

- extracting the compound from the reaction solution into a solvent;
- evaporating the solvent;
- adding an anti-solvent and/or cooling
- isolating the crystals formed, and optionally;
- ~~recrystallising~~ recrystallizing the crystals formed ~~in step c);~~ or isolated ~~in step d).~~

24. (Currently Amended) The process according to ~~any one of claims 1 to 23~~
claim 1, ~~whereby~~ wherein the chemical purity of Form A of compound IVa is above 95%.

25. (Currently Amended) A process for the ~~manufacturing~~ manufacture of NO
donating ketoprofen of formula IVd comprising:

~~step 1~~ (1), reacting a compound of formula Id with 1,3-propanediol to obtain a
compound of formula IId,

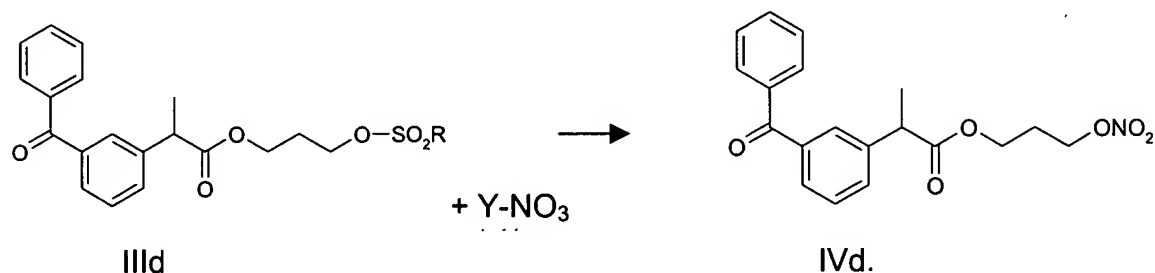


~~followed by,~~

~~step 2~~ (2), reacting the compound of formula IId with RSO_2Cl , wherein R is as defined in
claim 1, to obtain a compound of formula IIId,



~~step 3~~ (3), reacting the compound of formula IIId with a nitrate source Y-NO_3 , wherein Y
is as defined in claim 1, to obtain a compound of formula IVd,



26. (Currently Amended) The process according to claim 25, ~~for the manufacturing of~~ wherein the compound of formula IVd is the S-enantiomer of NO donating ketoprofen of formula IVd.

27. (Original) 2-[2-(nitrooxy)ethoxy]-ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (IVa) in a substantially crystalline form.

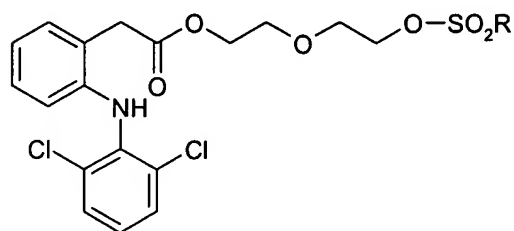
28. (Currently Amended) The compound according to claim 27 in ~~anhydrate~~ anhydrous form.

29. (Currently Amended) The compound according to claim 27, characterised characterized by the major peaks in the X-ray powder diffractogram shown in the table below:

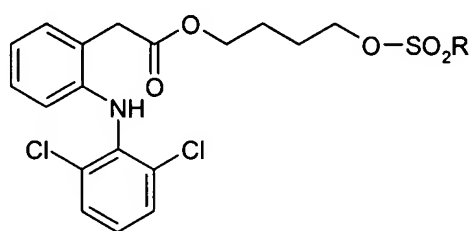
D /Å	Relative		D/Å	Relative
12.7	M		3.52	M
8.7	W		3.49	M
8.1	W		3.44	W
6.3	S		3.41	VS
5.94	M		3.31	W
5.91	M		3.28	M
5.58	M		3.17	S
5.34	M		3.15	S
5.05	W		3.13	W
4.50	S		3.06	M
4.48	S		3.04	W
4.38	M		2.97	M
4.35	M		2.96	M
4.28	M		2.81	W
4.23	S		2.70	M
4.08	S		2.68	M
4.06	S		2.64	M
3.96	S		2.60	W
3.78	S		2.54	W
3.76	S		2.43	W
3.55	W			

30. (Currently Amended) The compound according to claim 27, characterised characterized by having a monoclinic unit cell with parameters $a = 13.79 \text{ Å}$, $b = 11.90 \text{ Å}$, $c = 13.01 \text{ Å}$, $\alpha = 90^\circ$, $\beta = 94.0^\circ$, $\gamma = 90^\circ$.

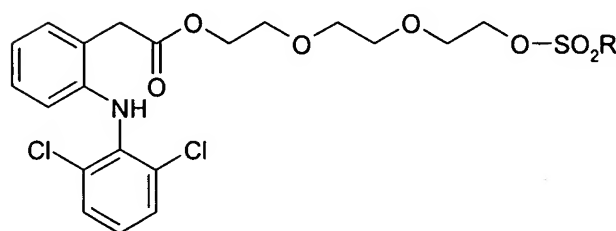
32. (Currently Amended) Compounds of formula IIIa, IIIb, IIIc and IIId:



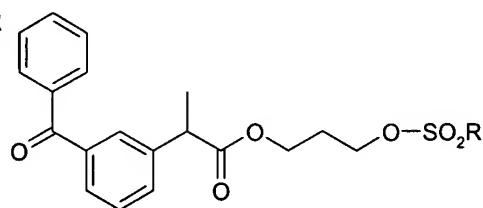
IIIa



IIIb



IIIc



111d

33. (Currently Amended) Use of the process according to ~~any one of claims 1 to 21~~ claim 1 for the large scale manufacturing of the compounds of formula IVa, IVb, IVc and IVd.

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35. (Original) Use of intermediate compounds of formula IIIa, IIIb, IIIc and IIId as defined in claim 32, prepared according to the process described under step 1 and 2 of claim 1, for the manufacturing of a medicament for the treatment of pain and/or inflammation.

36. (Original) Use of Form A of compound IVa for the manufacturing of a medicament.

37. (Original) Use of Form A of compound IVa for the manufacturing of a medicament for the treatment of pain and/or inflammation.

38. (Original) A pharmaceutical formulation comprising a therapeutically effective amount of Form A of compound IVa, optionally in association with diluents, excipients or carriers.